

Various metabolic risk factors could be linked to diabetes-related pain with major implications for treatment

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Around 1 in 50 people in the general population and 1 in 6 of those aged over 40 years experience neuropathy (damage to the nerves of the peripheral nervous system), which can cause numbness, tingling, pain, or weakness. The most common cause of neuropathy is diabetes, and up to half of diabetes patients can be affected. Currently, among the only treatments for neuropathy are glucose control (which often only delays it) and pain management. Yet less than half of patients are treated for pain, despite the availability of many effective therapies. Growing evidence suggests that various metabolic risk factors, including prediabetes, could be linked with neuropathy and thus be targets for new disease-modifying drugs. The issues are discussed in a Review in the June issue of *The Lancet Neurology*, by Dr Brian C Callaghan and colleagues, all of the University of Michigan, Ann Arbor, MI, USA.

Diabetes can cause various patterns of so-called [diabetic neuropathy](#), but the most common presentation is a distal symmetrical polyneuropathy (DSP), in which symptoms begin in the feet and spread up the limbs. Patients experience decreased quality of life, both physically and mentally. DSP can cause [balance problems](#), which may lead to falls. Neuropathy is one of three main [risk factors](#) for falls in patients with diabetes, along with [retinopathy](#) and vestibular dysfunction. Patients with diabetic DSP are two to three times more likely to fall than those with diabetes and no neuropathy. Additionally, patients with severe DSP are at risk of ulcerations and lower-extremity amputations, with 15% developing an ulcer during the course of their disease. Diabetes is the leading cause of lower-extremity amputations, roughly 80 000 of which are undertaken in the USA every year in patients with the disorder. Indeed, patients with diabetes are 15 times more likely than people without diabetes to have this life-changing

complication.

Overall, costs associated with diabetic neuropathy in the USA are estimated to be between 4.6 and 13.7 billion dollars, with most of the expense attributed to those with type 2 diabetes. Therefore, neuropathy is associated with a quarter of the total costs of diabetes care in the USA.

Since the data linking prediabetes (a condition with higher than normal blood sugar levels, but not yet high enough for a diabetes diagnosis) with neuropathy are conflicting, a comprehensive study is needed to establish whether or not it is one of the metabolic drivers that underlie the onset and progression of neuropathy. The answer has direct implications for potential therapies for many patients with neuropathy. Currently one third of adult Americans meet criteria for prediabetes, but less than 5% of these people have received a formal diagnosis of prediabetes from their health-care providers and only a small percentage are being treated. Establishing a causal relation between prediabetes and neuropathy would change the clinical management of a substantial number of patients.

Research suggests that various metabolic factors (components of 'metabolic syndrome') other than blood [glucose control](#)-such as levels of LDL (bad) cholesterol and high blood pressure-might have a role in the development of neuropathy. The authors say that there are promising lines of investigation that could lead to improved prevention and treatment of the disorder. The magnitude of the effect of glucose control on neuropathy is much smaller in patients with type 2 diabetes than in those with type 1 diabetes. In view of this small effect size and the fact that many patients with type 2 diabetes continue to develop neuropathy despite adequate glucose control, discovery of modifiable

risk factors for neuropathy is essential. Callaghan and colleagues are currently conducting such a study.

The authors conclude: "Components of the metabolic syndrome, including prediabetes, are potential risk factors for neuropathy, and studies are needed to establish whether they are causally related to neuropathy. These lines of enquiry will have direct implications for the development of new treatments for diabetic neuropathy."

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